UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: December 12, 2013

SUBJECT: **Picloram.** Human Health Assessment Scoping Document in Support of Registration Review.

PC Code: 005104
Decision No.:
Petition No.: NA

Risk Assessment Type: NA
TXR No.: NA

MRID No.: NA

DP Barcode: D413166
Registration No.: NA
Regulatory Action: Registration Review Scoping Document
Case No.: 96
CAS No.: 1918-02-1 (picloram acid); 2545-60-0 (potassium salt); 67534-47-5 (triisopropanolamine)
40 CFR: §180.292

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Attached is the Health Effects Division's (HED) human health risk assessment scoping document for the herbicide picloram and associated salts to support registration review.

Executive Summary

The Health Effects Division Picloram Risk Assessment Team has evaluated the database and the most recent human health risk assessments for the herbicide picloram and associated salts and esters (picloram potassium salt, picloram triisopropanolamine salt, triethylamine salt and isooctyl ester). HED performed this evaluation in order to determine the scope of work necessary to support the established tolerances and existing registrations. The primary source of information for this evaluation was the most recent human health risk assessment written for the chemical (Memo, D207989, P. Hurley *et al.*, 27 July 1998). However, it should be noted that since the 1998 review, triethylamine salt and isooctyl ester are no longer registered. Therefore, for purposes of this assessment, picloram will refer to picloram acid, and its associated potassium and triisopropanolamine salts. There have been no new requests for uses, pending products or other Pesticide Regulatory Improvement Act (PRIA) actions associated with picloram.

Picloram is a synthetic auxin and this type of herbicide kills susceptible plants by mimicking the plant growth hormone auxin (indole acetic acid). Applications of picloram at effective rates causes uncontrolled and disorganized plant growth that leads to plant death (Tu et al., 2001). Picloram is a restricted-use chemical with long-term residual effects.

Picloram was first registered for use on woody plants and broadleaf weeds on rangeland, grass pastures, fallow, wheat, barley, oats, forest and other non-crop areas in 1964. Subsequent registrations were allowed for picloram use on: non-agricultural sites, rights-of-way, industrial sites, storage yards, fencerows, industrial storage areas, and hedgerows.

The toxicology database for picloram is complete and no additional toxicity studies are required. HED's Hazard and Science Policy Council (HASPOC) determined a subchronic inhalation study, an acute neurotoxicity study, and a subchronic neurotoxicity study are not required for picloram (K. Rury, TXR#0056802, 17 October 2013). The toxicology database for picloram includes studies with all derivatives of picloram, including the technical product (picloram acid) and its salts (picloram potassium salt and picloram triisopropanolamine salt).

There is no evidence of neurotoxicity in the available toxicology studies and no developmental concern; therefore, HED previously concluded that a developmental neurotoxicity (DNT) study was not required. HED still supports the conclusion that a DNT is not needed since there is no concern for susceptibility. During registration review, HED will update the hazard characterization, points of departure and endpoints as needed based on current policies and risk assessment methodologies.

Since the last risk assessment, an immunotoxicity study and bacterial reverse mutation assay were submitted and reviewed. HED concludes that the new immunotoxicity study and the bacterial reverse mutation assay have no impact on the overall assessment and will not affect the toxicological endpoints. The toxicology studies with picloram indicate that the main target organs in the rat and dog were liver and kidney following administration in subchronic and chronic studies. There is no evidence of neurotoxicity, carcinogenicity or qualitative or quantitative susceptibility of the developing fetus or offspring, based on results from the developmental, reproductive or carcinogenic toxicity studies. Therefore, based on the

completeness of the database, the lack of susceptibility, the lack of neurotoxicity and the conservative nature of the exposure assessment, HED continues to support the previous recommendation to reduce the required 10X Food Quality Protection Act (FQPA) Safety Factor to 1X.

The residue chemistry database for picloram is complete for the purpose of supporting the currently registered uses. No new residue chemistry data are required. The residues of concern in plants and livestock commodities are parent picloram as well as the impurity hexachlorobenzene (HCB). Previously, HED did not separate the residues of concern to be used for risk assessment from those used for tolerance enforcement. HED now concludes that for risk assessment purposes picloram and HCB should be included; however, only picloram should be used for tolerance enforcement. This conclusion is consistent with the approach taken previously and no revisions to the existing tolerances or tolerance expression are required.

The dietary exposure database is adequate to support the existing registrations and tolerances. During registration review, it is expected that the Environmental Fate and Effects Division (EFED) will provide new drinking water estimates, including any new drinking water degradates from hydrolysis. A new dietary exposure assessment will be conducted during registration review incorporating these revised drinking water residue estimates. However, based on the results of earlier risk assessments, HED does not anticipate risks of concern from chronic dietary exposure to picloram, including drinking water. In previous assessments all dietary risk estimates were less than 1% of the chronic population-adjusted dose and were, therefore, well below HED's level of concern. HED recently updated its dietary model to incorporate more recent consumption data from the National Health and Nutrition Examination Survey (NHANES). This new version of the model will be used during registration review for the new dietary assessment.

While there are currently no registered residential uses of picloram, residential bystander exposures resulting from off-site transport (i.e., spray drift or volatilization) may occur as a result of occupational applications of picloram. The need for a bystander risk assessment for picloram will be considered during registration review.

Occupational handler exposures resulting from agricultural and non-agricultural uses of picloram have not been evaluated quantitatively in Agency memoranda, due to the lack of dermal and inhalation endpoints. During registration review, HED will update the occupational handler assessment as necessary with current policies and revised toxicological endpoints and doses. A dermal handler assessment will not be conducted based on the lack of systemic toxicity in the dermal studies, and the lack of neurotoxicity or developmental effects in other toxicological studies. However, a non-cancer inhalation handler assessment will be conducted during registration review, using an endpoint and dose to be selected from an oral study. Cancer handler risk estimates for the HCB impurity were previously assessed and resulted in cancer risk estimates ranging from 4.4×10^{-9} to 3.6×10^{-8}. HED does not anticipate the need to update handler cancer exposure risk estimates for HCB during registration review.

Chemical-specific dislodgeable foliar residue (DFR) data have not been submitted, but are not needed due to the lack of an endpoint for dermal risk assessment. During registration review,

HED will consider the impact of new policies and procedures, such as addressing volatilization exposure, as well as the potential for exposure from spray drift. However, no risk issues are expected and no data are needed at this time for picloram. A dermal post-application cancer assessment for the impurity HCB was not previously conducted, and may be needed during registration review.

Introduction

This document summarizes HED's evaluation of the data available for assessing human health risk from exposure to the herbicide picloram, as well as any data needed to support registration review. Picloram is an herbicide used to control a variety of annual and perennial broadleaf weeds and woody species. Picloram is readily absorbed by plant roots, foliage, and it is readily translocated throughout the plant. It can persist in an active form in the soil from several months to years, and can also be released from the roots of treated plants into the soil, where other non-target species may take it up and be injured or killed (Hickman et al. 1990). In conducting this evaluation, HED has considered the most recent human health risk assessment (D207989; P. Hurley; 27 July 1998), HED and OPPIN/PRISM databases, open literature (via Google Scholar) and the latest Agency science policies and risk assessment methodologies.

The structure of picloram and its associated salts and esters, as well as the chemical names and other identifiers, can be found in the chemical identity table attached to this document (Attachment 1). A list of the active and conditional registrations is provided in Attachment 5.

Hazard Identification/Toxicology

The herbicidal mode of action for picloram is that of a plant growth regulator. Picloram disrupts normal growth by acting like a class of plant growth hormones known as auxins. This leads to uncontrolled and abnormal plant growth which results in toxicity or death of the plant. The toxicological mode of action in mammals is unknown.

The toxicology database for picloram is complete and no additional toxicity studies are required. HED's Hazard and Science Policy Council (HASPOC) determined a subchronic inhalation study, an acute neurotoxicity study, and a subchronic neurotoxicity study are not required for picloram (K. Rury, TXR#0056802, 17 October 2013). The toxicology database for picloram includes studies with all derivatives of picloram, including the technical product (picloram acid), its salts (picloram potassium salt and picloram triisopropanolamine salt) and ester (picloram isooctyl ester). Although picloram isooctyl ester is no longer registered, toxicology studies with the ester still provide useful information based on the structural similarity and similar toxic effects observed compared to the other derivatives of picloram.

HED previously determined that a DNT study is not required based on the overall toxicity database and weight of evidence, including the lack of neurotoxicity observed in subchronic or chronic studies in rats, mice, and dogs and the lack of developmental toxicity in the rat and rabbit (D207989, P. Hurley, 7/27/1998). Additionally, there is no concern for increased susceptibility

of the young to picloram. HED continues to support this conclusion, and will not require the DNT study during registration review.

In the most recent risk assessment (D207989, P. Hurley, 7/27/1998), no dermal or inhalation risk assessment was required due to the lack of an appropriate endpoint. No systemic or dermal toxicity was observed in the submitted 21/28-day dermal toxicity studies. In addition, no evidence of neurotoxicity or developmental effects was observed in the toxicity database. Therefore, a dermal risk assessment is still not required. In contrast, based on current policies and risk assessment methodologies, an endpoint for assessing inhalation exposure and risk is chosen from an oral study in the absence of a route specific endpoint. During registration review, HED will choose an oral endpoint and dose of the appropriate duration for assessing inhalation exposure.

An immunotoxicity study was recently submitted and has been reviewed by HED (MRID 49021001). The study is acceptable and the results show no evidence of immunotoxicity for picloram. These results are consistent with the existing toxicological database which does not indicate that the chemical targets the immune system. Given the above information, HED concludes that this new immunotoxicity study has no impact on the overall hazard characterization, doses and endpoints selected (along with traditional uncertainty factors) for risk assessment.

A bacterial reverse mutation assay (MRID 47296102 and 47296103) was recently submitted. This study will be reviewed as part of registration review. A preliminary review indicates that the study result is negative for mutagenicity. In addition, an acceptable bacterial reverse mutation assay was already available for picloram. Given the above information, HED concludes that this new bacterial reverse mutation assay has no impact on the overall assessment.

Picloram appears to target the liver and kidney following administration in subchronic and chronic studies. In subchronic studies, the most frequent effects observed were increased liver weight (rat and dog), hepatocellular hypertrophy (rat), and increased kidney weights (rat). In most studies the effects on the liver were not corroborated by any other signs of liver toxicity and are indicative of an adaptive response at the doses tested. However, in one subchronic study in rats, increased levels of cholesterol and alanine aminotransferase were observed at the highest dose tested, indicative of an adverse effect on the liver General signs of toxicity (decreased body weight, body weight gain, and food consumption) were only observed in the subchronic dog study. In chronic studies, similar findings were observed in dogs (increased liver weights), mice (increased kidney weights), and rats (increased liver weight, liver hypertrophy, and increased kidney weights). Additional effects on the kidney were observed in the rat following chronic exposure, including blood in the urine, increased serum phosphorus, and unilateral or bilateral papillary necrosis.

There was no evidence of increased pre- and/or postnatal quantitative and qualitative susceptibility in the rat or rabbit. No effects in the offspring were observed in the prenatal developmental toxicity studies in rats and rabbits and the two-generation reproduction study in rats.

There was no evidence of carcinogenicity seen in mice and rats following administration of picloram acid or picloram potassium salt. Carcinogenicity studies are not available for the other derivatives of picloram. The 2-ethylhexanol was reported to be a metabolite of picloram isooctyl ester and is also a metabolite of di-(2-ethylhexyl)phthalate, where it is believed to play a role in the ability of di-(2-ethylhexyl)phthalate to cause peroxisome proliferation leading to carcinogenicity. However, the potential of picloram isoctyl ester to be carcinogenic is not a concern because it is no longer registered and 2-ethylhexanol is not a metabolite of the currently registered forms of picloram. Hexachlorobenzene (HBC), a recognized impurity in picloram compounds at 0.01% or lower, is considered to be an animal carcinogen and a probable human carcinogen. Thus, despite picloram not displaying any evidence of carcinogenicity in animal studies, there is still a potential cancer risk based on the presence of HCB in picloram formulations. All forms of picloram were not mutagenic or clastogenic. An acceptable rat metabolism study for picloram is available.

Picloram has low acute toxicity in lethality studies via oral exposure in the rat (Toxicity Category III-IV) and dermal exposure in the rabbit (Toxicity Category III). Picloram was classified as Toxicity Category I-II for inhalation exposure in rats but this was influenced by the highest practically obtainable concentrations in the studies. Picloram is likely less toxic by acute inhalation because no deaths and minimal clinical signs were observed in the studies and the end use product was classified as Toxicology Category IV via inhalation exposure. Picloram was a moderate eye irritant (Toxicity Category III), was not a dermal irritant (Toxicity Category IV), and the salts, but not the technical, were dermal sensitizers.

In the most recent risk assessment, the required 10X FQPA safety factor was reduced to 1X based on: 1) the lack of increased pre- and postnatal susceptibility of rats to in utero and/or postnatal exposure in the developmental and reproductive toxicity studies; 2) there is no evidence of neurotoxicity in the database and 3) the risk assessment does not underestimate exposure, since the dietary assessment is based on conservative assumptions such as tolerance-level residues in foods and upper-bound modeled estimates of residues in drinking water. In addition, there are no registered residential uses for picloram. These conclusions are not expected to change during registration review. The toxicological endpoints and doses used in the most recent human health risk assessment are summarized in Attachment 3. The toxicity profile of picloram is summarized in Attachment 4.

Conclusions for Hazard Identification/Toxicology

The toxicity database is complete for the purpose of registration review, and is appropriate for assessment of potential carcinogenic, mutagenic, developmental, and reproductive effects. In the most recent risk assessment, the FQPA safety factor was reduced to 1X based on a number of factors including the lack of susceptibility in developmental and reproduction studies in rats, the lack of observed neurotoxicity, and the conservative assumptions used in the exposure assessments. HED continues to support the previous recommendation to reduce the required 10X Food Quality Protection Act (FQPA) Safety Factor to 1X. During registration review, HED will consider the appropriateness of the existing endpoints based on current policies and risk assessment methodologies. HED anticipates updating the endpoints and points of departure for the subchronic and chronic oral studies; in some cases the endpoints and points of departure were

based on effects that HED does not consider adverse (such as hepatocellular hypertrophy in the absence of other liver effects). Finally, picloram has multiple picloram acid technical products which are considered substantially similar but have different acute toxicity profiles. During registration review, HED will consider all of the available data on the acute toxicity of picloram to support risk assessment.

Dietary Exposure

Tolerances for picloram are listed in 40 CFR 180.292 and range from 0.05 to 400 ppm. The residue chemistry database for picloram is complete for the purpose of supporting the currently registered uses. HED previously determined that the residues of concern in plants and livestock commodities are the parent picloram as well as the impurity HCB. In earlier risk assessments, HED did not separate the residues of concern to be used for risk assessment from those used for tolerance enforcement. Based on a review of the available data and the tolerance definition, HED now concludes that picloram and HCB should be included for risk assessment whereas picloram only should be used for tolerance enforcement. This conclusion is consistent with the approach taken previously and no revisions to the existing tolerances or tolerance expression are required.

Dietary exposure estimates in the previous risk assessment assumed tolerance-level residues on food commodities and do not include direct incorporation of potential residues in drinking water. These dietary exposure estimates were partially refined to incorporate percent crop treated data on available food commodities. All dietary risk estimates were less than 1% of the chronic population-adjusted dose and were, therefore, well below HED's level of concern. No acute dietary endpoint was identified for picloram; therefore, no acute dietary exposure assessment was necessary.

Picloram is persistent, highly mobile and stable to hydrolysis; therefore, it is expected that picloram will be present in groundwater. At present, the residues of concern in drinking water are parent picloram and the impurity HCB. During registration review, it is expected that EFED will provide new drinking water estimates, including any new drinking water degradates from hydrolysis. Should major new drinking water degradates be identified, the residues of concern may be revised to include these degradates. Therefore, a new dietary exposure assessment will be conducted during registration review, directly incorporating these revised drinking water residues into this updated assessment. However, based on the results of earlier risk assessments, HED does not anticipate risks of concern from chronic dietary exposure to picloram including drinking water.

Picloram has been classified as "Group E - Evidence of non-carcinogenicity for humans." Therefore, a carcinogenic dietary risk assessment is not required for the parent picloram. However, the impurity HCB is classified as a group B2 carcinogen with a cancer slope factor (Q*) of 1.02 (mg/kg bodyweight per day)$^{-1}$. Prior risk assessments included a cancer dietary exposure assessment using this Q*, with the assumption that the HCB impurity does not exceed 0.01% of the technical product. HED has evaluated the currently registered products and concluded that the HCB content remains the same. The cancer dietary risk estimate from HCB in the most recent risk assessment was 1.5×10^{-7}.

Since the last dietary assessment, HED updated its dietary model to incorporate more recent consumption data from the National Health and Nutrition Examination Survey (NHANES). In addition, updated percent crop treated data are available for refining residue exposure estimates and will be incorporated as needed if an updated dietary exposure assessment is conducted.

Conclusions for Dietary Exposure

The dietary exposure database is adequate to support the existing registrations and tolerances. No new residue chemistry data are required. A new dietary assessment will be needed and will incorporate the following as needed: any new data identified which impact dietary exposure estimates, including those from drinking water; new toxicological points of departure are identified, including revisions to the FQPA SF; OPP dietary exposure policies and procedures are revised. HED recently updated its dietary model to incorporate more recent consumption data from the National Health and Nutrition Examination Survey (NHANES). This new version of the model will be used during registration review for the updated dietary assessment.

Residential Exposure

There are currently no proposed or registered residential uses associated with picloram. However, residential exposures resulting from off-site transport (e.g., spray drift or volatilization) may occur as a result of picloram applications to agricultural fields. The need for a bystander risk assessment for picloram will be considered during registration review.

Spray Drift

Residential exposures resulting from off-site transport (e.g., spray drift or volatilization) might occur as a result of applications of picloram. The Agency is in the process of evaluating these types of exposures and might, as appropriate, develop policies and procedures to identify the need for and, subsequently, the way to incorporate these post-application exposures into the Agency's risk assessments. The need for spray drift and volatilization risk assessment for picloram will be examined during registration review.

Conclusions for Residential Exposure

There are currently no proposed or registered residential uses associated with picloram. However, HED will consider the impact of a potential new dermal POD and new policies and procedures, such as addressing volatilization exposure, as well as the potential for exposure from spray drift, during registration review.

Aggregate Risk Assessment

In the most recent risk assessment no acute, dermal or inhalation endpoints and doses were selected. Due to the lack of an acute endpoint, there were no acute aggregate risks associated with picloram. There are currently no proposed or registered residential uses associated with picloram; therefore, a short-term aggregate risk assessment is not applicable. Chronic aggregate risk estimates were equivalent to the chronic dietary risks, and were not of concern.

Conclusions for Aggregate Assessment

HEDs previous conclusions, (i.e., no risks of concern) regarding aggregate risks are not expected to change during registration review.

Occupational Exposure and Risk

Picloram is a systemic herbicide, used for control of woody plants and wide range of broadleaf weeds in range management programs. It is a restricted use chemical based on its phytotoxicity to non-target plants and is formulated as emulsifiable, soluble concentrate, and as a ready-to-use solution. Picloram may be applied as a broadcast, spot treatment, or foliar application using aerial, ground, and hand-held spray equipment. The personal protective equipment (PPE) required for handlers consists of a single layer of clothing (long sleeve shirt, long pants, and socks plus shoes) and chemical resistant gloves. The restricted entry interval (REI) for picloram is 12 hours.

The agricultural (i.e., barley, follow, oats, wheat pastureland and forests) and non-agricultural (i.e., rights-of-way, industrial sites, pipelines, railroads, storage yards, fencerows, and hedgerows) use sites of picloram result in short-term (1 - 30 days) and intermediate-term (1 - 6 months) occupational exposures.

Occupational Handler Exposure

The registrant has not submitted chemical-specific exposure data to estimate handler exposures. In the absence of chemical-specific data, it is HED policy to use the best available data to assess handler exposures. Sources of such generic (surrogate) handler data include Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1), and the Agricultural Handler Exposure Task Force (AHETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

For risk assessments conducted prior to 2013, endpoints and doses were not selected for dermal or inhalation exposure assessments based on a lack of toxicity. Therefore, handler exposures resulting from agricultural and non-agricultural uses of picloram have not been evaluated quantitatively in Agency memoranda. HASPOC has since determined a subchronic inhalation study, an acute neurotoxicity study, and a subchronic neurotoxicity study are not required for picloram (K. Rury, TXR#0056802, 17 October 2013). Since no systemic or dermal toxicity was observed in the submitted 21/28-day dermal toxicity studies and there was no evidence of neurotoxicity or developmental effects was observed in the toxicity database, a dermal risk assessment is still not required. In contrast, based on current policies and risk assessment methodologies, an endpoint and dose for inhalation exposure and risk assessment is chosen from an oral study in the absence of a route specific endpoint. Therefore, a quantitative non-cancer occupational handler assessment for picloram will be required during registration review.
The cancer handler risk estimates for the HCB impurity were previously assessed and resulted in cancer risk estimates ranging from 4.4×10^{-9} to 3.6×10^{-8}. HED does not anticipate the need to update handler exposure risk estimates for HCB during registration review.

Occupational Post-application Exposure

In the absence of toxicity via the dermal route, a quantitative dermal post-application risk assessment will not be conducted for the agricultural and non-agricultural uses of picloram. Furthermore, the REI on registered labels is considered appropriate based on the toxicity of the technical ingredient. Although, HED would typically require dislodgable foliar residue (DFR) studies based on the existing use pattern; DFR studies are not required due to lack of toxicity via the dermal route.

A dermal post-application cancer assessment for the impurity HCB was not previously conducted, and may be needed during registration review.

A quantitative post-application inhalation exposure assessment was not performed for picloram or the impurity HCB based on the Agency's current practices. However, there are potential sources of inhalation exposure to workers performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and re-suspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (*http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html*). The Agency is in the process of evaluating the SAP report as well as available post-application inhalation exposure data generated by the Agricultural Reentry Task Force and may, as appropriate, develop policies and procedures, to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for picloram.

Although a quantitative post-application inhalation exposure assessment was not performed for picloram and HCB, the handler assessment to be conducted during registration review is considered protective of potential post-application exposure for workers.

Conclusions for Occupational Exposure and Risk

A non-cancer dermal handler assessment for picloram will not be conducted as there is no dermal toxicity. However, a non-cancer inhalation handler assessment will be conducted for picloram incorporating the new selected inhalation endpoint and dose, and updated policies for risk assessment during registration review. Based on the previously calculated cancer handler risk estimates associated with the impurity HCB, HED does not anticipate the need to update the cancer handler exposure risk estimates for HCB during registration review. In the absence of toxicity via the dermal route, a quantitative dermal post-application risk assessment for picloram will not be conducted. A DFR study is not required for picloram in order to assess post-application exposure and risk. Occupational cancer risk associated with post-application exposure to the impurity HCB may need to be assessed during registration review.

Public Health and Pesticide Epidemiology Data

Based on the low frequency of incident cases reported for picloram in both IDS and SENSOR-Pesticides, there does not appear to be a concern at this time that would warrant further investigation. The Agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be included in the risk assessment. A summary report listing incidents reported to EPA for picloram will be provided for the docket. The reported incidents will be screened in more detail during the development of the Final Work Plan for picloram.

Tolerance Assessment and International Harmonization

The qualitative nature of the residue for the existing uses has been adequately delineated based upon an adequate metabolism studies in wheat (memo, P. Hurley, 07/27/98, D207989). Tolerances for residues of picloram are listed under 40 CFR §180.292(a)(1). HED previously determined that the residues of concern in plants and livestock commodities are parent picloram as well as the impurity hexachlorobenzene (HCB). In earlier risk assessments, HED did not separate the residues of concern to be used for risk assessment from those used for tolerance enforcement. Based on a review of the available data and the tolerance definition, HED now concludes that picloram and HCB should be included for risk assessment whereas picloram only should be used for tolerance enforcement. This conclusion is consistent with the approach taken previously and no revisions to the existing tolerances or tolerance expression are required. If the use pattern were to expand in the future to include additional crops, additional plant metabolism studies may be required. Such revisions would occur during new-use risk assessments and would likely not need to be considered during registration review.

Adequate enforcement methods are available for the determination of residues of picloram *per se* in/on plant and animal commodities. The tolerances and tolerance expression for picloram are up to date with respect to both coverage and measurement, having been recently reassessed and updated as a post-RED decision (memo, R. Loranger, 11/19/09, D370690).

Currently, there are no established maximum residue limits (MRLs) for picloram in Codex. Using the same residue definition as the U.S., Canada has established picloram MRLs for barley and wheat grain, as well as in livestock commodities. In some cases, the Canadian MRLs are already harmonized with U.S. tolerances; in most other cases, the Canadian MRLs are lower than the U.S. tolerances. During registration review, HED will reconsider the U.S. tolerances and will harmonize them with Canadian MRLs to the extent possible.

The international residue limit status sheet can be found in Attachment 2.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf. As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established

procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures and risks based on home use of pesticide products for adult applicators and post-application activities for toddlers, youths, and adults entering or playing on treated areas are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Endocrine Disruptor Screening Program

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its most recent registration decision for picloram, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), picloram is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of

chemicals identified for EDSP screening was published on June 14, 2013[1] and includes some pesticides scheduled for Registration Review and chemicals found in water. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[2]

In the interim, EPA is making no human health or environmental safety findings associated with the EDSP screening of picloram. Before completing this Registration Review, the Agency will make an EDSP FFDCA section 408(p) determination.

Cumulative Risk Assessments

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to picloram and any other substances, and picloram does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that picloram has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's OPP concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

Human Studies

Past picloram risk assessments rely in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their dermal and inhalation exposure. These data, which include studies from the Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1); the Agricultural Re-entry Task Force (ARTF) database; and other registrant-submitted exposure monitoring studies, are subject to ethics review pursuant to 40 CFR 26, have received that review, and are compliant with applicable ethics requirements. For certain studies that review may have included review by the Human Studies Review Board. Descriptions of data sources as well as guidance on their use can be found at http://www.epa.gov/pesticides/science/handler-exposure-data.html and http://www.epa.gov/pesticides/science/post-app-exposure-data.html.

Data Requirements

- None

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[1] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.

[2] http://www.epa.gov/endo/

References

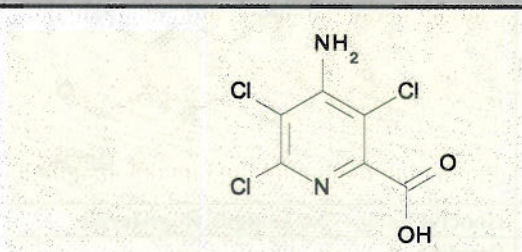
P. Hurley, et al, D207989, 7/27/1998, Picloram Potassium Salt. Human Health Risk Assessment for Grain Sorghum as a Rotational Crop. Amended Petition Proposing Tolerances for Inadvertent Residues of Picloram in or on Grain Sorghum.

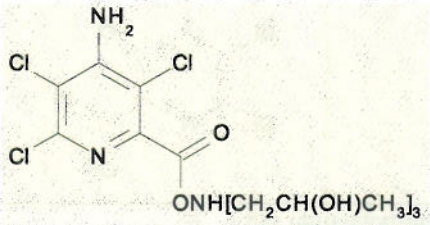
S. Ratnayake and J. Alsadek, 6/24/13, BEAD Chemical Profile (BCP) for Registration Review: Picloram Salts and Esters Case (005101, 005102 and005104)

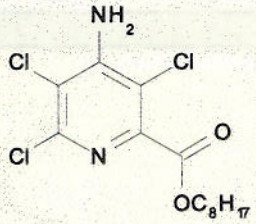
Attachments

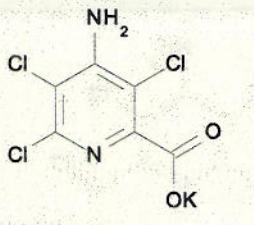
Attachment 1. Chemical Identity Table
Attachment 2. International Residue Limit Status
Attachment 3. Picloram Endpoint Selection Tables
Attachment 4. Picloram Toxicity Profiles
Attachment 5. Pending and Active Registrations for Ingredients

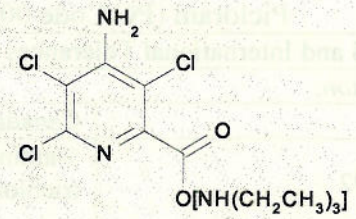
Attachment 1. Chemical Identity Table

Chemical Identity	
Chemical structure	
Common name	Picloram
Chemical Class	Pyridine
PC Code	005101
Company experimental name	
Molecular formula	$C_6H_3Cl_3N_2O_2$
Molecular weight	241.48
Vapor Pressure (35C)	6.16×10^{-7} mm Hg
IUPAC name	4-amino-3,5,6-trichloropyridine-2-carboxylic acid
CAS name	4-amino-3,5,6-trichloro-2-pyridinecarboxylic acid
CAS registry number	1918-02-1
Registration Review Case No.	96

Chemical Identity	
Chemical structure	
Common name	Triisopropanolamine salt
Chemical Class	Pyridine
PC Code	005102
Company experimental name	
Molecular formula	$C_{15}H_{24}Cl_3N_3O_5$
Molecular weight	432.6
Vapor Pressure (35C)	
IUPAC name	
CAS name	
CAS registry number	6753-47-5
Registration Review Case No.	96

Chemical Identity	
Chemical structure	
Common name	Isooctyl Ester – **No Longer Registered**
Chemical Class	Pyridine
PC Code	005103
Company experimental name	
Molecular formula	$C_{14}H_{19}Cl_3N_2O_2$
Molecular weight	353.5
Vapor Pressure (35C)	
IUPAC name	
CAS name	
CAS registry number	26952-20-5
Registration Review Case No.	96

Chemical Identity	
Chemical structure	
Common name	Picloram-potassium salt
Chemical Class	Pyridine
PC Code	005104
Company experimental name	
Molecular formula	$C_6H_2Cl_3N_2O_2$
Molecular weight	280.6
Vapor Pressure (35C)	
IUPAC name	potassium 4-amino-3,5,6-trichloropyridine-2-carboxylate or potassium 4-amino-3,5,6-trichloropicolinate
CAS name	4-amino-3,5,6-trichloro-2-pyridinecarboxylic acid monopotassium salt
CAS registry number	2545-60-0
Registration Review Case No.	96

Chemical Identity	
Chemical structure	
Common name	Picloram-triethylamine salt – **No longer Registered**
Chemical Class	Pyridine
PC Code	005105
Company experimental name	
Molecular formula	$C_{12}H_{18}Cl_3N_3O_2$
Molecular weight	342.5
Vapor Pressure (35C)	
IUPAC name	
CAS name	
CAS registry number	35832-11-2
Registration Review Case No.	96

Attachment 2. International Residue Limit (IRL) Status

Picloram (PC Code 005101; Date of Request 06-17-2013)

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[1]	Codex
40CFR §180.292 (a)General. (1) picloram (4-amino-3,5,6-trichloropicolinic acid)		4-amino-3,5,6-trichloropicolinic acid		None
Commodity	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[1]	Codex
Barley, grain	0.5	0.1		
Barley, pearled barley	3.0			
Barley, straw	1.0			
Cattle, fat	0.4	0.05		
Cattle, meat	0.4	0.05		
Cattle, meat byproducts	15	0.4 kidney of cattle 0.05 liver of cattle 0.4 meat byproducts of cattle		
Egg	0.05	0.05		
Goat, fat	0.4	0.05		
Goat, meat	0.4	0.05		
Goat, meat byproducts	15	0.4 kidney of goats 0.05 liver of goats 0.4 meat byproducts of goats		
Grain, aspirated fractions	4.0			
Grass, forage	400			
Grass, hay	225			
Hog, fat	0.05	0.05		
Hog, meat	0.05	0.05		
Hog, meat byproducts	0.05	0.4 kidney of hogs 0.05 liver of hogs 0.4 meat byproducts of hogs		
Horse, fat	0.4	0.05		
Horse, meat	0.4	0.05		
Horse, meat byproducts	15	0.4 kidney of horses 0.05 liver of horses 0.4 meat byproducts of horses		
Milk	0.25	0.05		
Oat, forage	1.0			
Oat, grain	0.5			
Oat, groats/rolled oats	3.0			
Oat, straw	1.0			
Poultry, fat	0.05	0.05		
Poultry, meat	0.05	0.05		
Poultry, meat byproducts	0.05	0.2 kidney of poultry, meat byproducts of poultry 0.05 liver of poultry		
Sheep, fat	0.4	0.05		
Sheep, meat	0.4	0.05		

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[1]	Codex
Sheep, meat byproducts	15	0.4 kidney of sheep 0.05 liver of sheep 0.4 meat byproducts of sheep		
Wheat, bran	3.0			
Wheat, forage	1.0			
Wheat, germ	3.0			
Wheat, grain	0.5	0.2		
Wheat, middlings	3.0			
Wheat, shorts	3.0			
Wheat, straw	1.0			
Completed by: M. Negussie; 06/19/2013				

[1] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

Attachment 3. Endpoint Selection Tables.

Table 1. Summary of Toxicological Doses and Endpoints for Picloram Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General population, including infants and children and females 13-49)	N/A	N/A	N/A	No appropriate endpoint is available.
Chronic Dietary (all populations)	NOAEL= 20 mg/kg/day	UF_A=10X UF_H=10X FQPA SF = 1X	Chronic RfD = 0.2 mg/kg/day cPAD = 0.2 mg/kg/day	Chronic feeding/carcinogenicity study in rats LOAEL = 60 mg/kg /day, based on increased size and altered staining properties of centrilobular hepatocytes and increased absolute and/or relative liver weights in both sexes.
Cancer (oral, dermal, inhalation)	Classification: Group E-evidence of non-carcinogenicity for human.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower, environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (c = chronic). RfD = reference dose. N/A = not applicable.

Table 2. Summary of Toxicological Doses and Endpoints for Picloram Use in Occupational Human Health Risk Assessments

Exposure Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short-Term (1 - 30 days) and Intermediate-term (1 - 6 months)	N/A	N/A	N/A	No appropriate endpoint is available.
Inhalation Short-Term (1 - 30 days) and Intermediate Term (1-6 months)	N/A	N/A	N/A	No appropriate endpoint is available.
Cancer (oral, dermal, inhalation)	Classification: Group E-evidence of non-carcinogenicity for human.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower, environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L= use of a LOAEL to extrapolate a NOAEL . MOE = margin of exposure. LOC = level of concern.

Attachment 4. Toxicity Profiles

Acute Toxicity -Picloram, Acid (94.1% a.i.)		
Test	**Result**	**Category**
Oral LD_{50} (rat)[1]	> 5000 mg/kg (males) 4012 mg/kg (females)	IV III
Dermal LD_{50} (rabbit)[2]	> 2000 mg/kg (both sexes)	III
Inhalation LC_{50} (rat)[3]	> 0.035 mg/L (both sexes)	I
Eye Irritation[4]	Moderate eye irritant	III
Dermal Irritation[5]	Non irritant	IV
Dermal Sensitization[6]	Non sensitizer	N/A
Delayed Neurotoxicity	Not conducted	N/A

[1-6]MRID#s 404794-13 thru -18

Acute Toxicity -Picloram Potassium Salt (38.8% a.i.)		
Test	**Result**	**Category**
Oral LD_{50} (rat)[7]	> 5000 mg/kg (males) 3536 mg/kg (females)	IV III
Dermal LD_{50} (rabbit)[8]	> 2000 mg/kg (both sexes)	III
Inhalation LC_{50} (rat)[9]	> 1.63 mg/L (both sexes)	II
Eye Irritation[10]	Moderate eye irritant	III
Dermal Irritation[11]	Non irritant	IV
Dermal Sensitization[12]	Positive skin sensitizer	N/A
Delayed Neurotoxicity	Not conducted	N/A

[7-12]MRID#s 404794-01 thru -06

Acute Toxicity -Picloram, Triisopropanolamine Salt (61% a.i.)		
Test	**Result**	**Category**
Oral LD_{50} (rat)[19]	> 5000 mg/kg (both sexes)	IV
Dermal LD_{50} (rabbit)[20]	> 2000 mg/kg (both sexes)	III
Inhalation LC_{50} (rat)[21]	> 0.07 mg/L (both sexes)	II
Eye Irritation[22]	Minimal irritant (both sexes)	III
Dermal Irritation[23]	Slight irritant (females) Not an irritant (males)	IV
Dermal Sensitization[24]	Positive	N/A
Delayed Neurotoxicity	Not conducted	N/A

[19-24]MRID#s 413812-01 thru -06

Picloram, Isooctyl ester (IOE) (85.9% a.i.)		
Test	**Result**	**Category**
Oral LD_{50} (rat)[13]	> 3500 mg/kg (both sexes)	III
Dermal LD_{50} (rabbit)[14]	> 2000 mg/kg (both sexes)	III
Inhalation LC_{50} (rat)[15]	>0.35 mg/L (both sexes)	II
Eye Irritation[16]	Moderate eye irritation	III
Dermal Irritation[17]	Mild dermal irritation	III
Dermal Sensitization[18]	Positive skin sensitizer	N/A
Delayed Neurotoxicity	Not conducted	N/A

[13-18]MRID#s 404794-07 thru -12

Subchronic, Chronic and Other Toxicity Profile for Picloram		
GDLN	STUDY	RESULTS
870.3100	Subchronic feeding in rats (13 weeks) MRID #: 00110537 Date: 1982 Core Grade: Minimum	**Picloram acid** NOEL: 50 mg/kg/day LOEL: 150 mg/kg/day Effects: liver weight increases and minimal microscopic changes in the liver.
870.3100	Subchronic feeding in rats (13 weeks) MRID #: 42297001 Date: 1991 Core Grade: Minimum	**Picloram isooctyl ester** NOEL: 73 mg/kg/day LOEL: 220 mg/kg/day Effects: increased liver weights accompanied by slight/very slight hepatocellular hypertrophy and increased kidney weights in males only.
870.3100	Subchronic feeding in rats (13 weeks) MRID #: 41442701 Date: 1990 Core Grade: Guideline	**Picloram triisopropanolamine salt** NOEL: 90 mg/kg/day LOEL: 550 mg/kg/day Effects: hepatocellular hypertrophy at 550 mg/kg/day and above (M; F at 1800 mg/kg/day); decreased body weight gain (M&F) and increased liver and kidney weights (F) at 1800

Subchronic, Chronic and Other Toxicity Profile for Picloram		
GDLN	STUDY	RESULTS
		mg/kg/day.
870.3150	Subchronic feeding in dogs (6 months) MRID # 00110534 Date: 1982 Core Grade: Minimum	**Picloram acid** NOEL: 35 mg/kg/day LOEL: 175 mg/kg/day Effects: decreased mean body weight gain & food consumption. Increased liver weights.
870.3200	21-day dermal in rabbits MRID #: 41384901 Date: 1990 Core Grade: Minimum	**Picloram potassium salt** NOEL for systemic effects: > 753mg/kg/day [Maximum amount of test material that could be practically maintained at the test site]. Effects: No systemic toxicity at any dose tested.
870.3200	21-day dermal in rabbits MRID #: 41384901 Date: 1990 Core Grade: Guideline	**Picloram triisopropanolamine salt** NOEL for systemic effects > 1320 mg/kg/day [limit test] Effects: No systemic toxicity at any dose tested.
870.3200	21-day dermal in rabbits MRID #'s: 42171601; 42870701 Date: 1991 Core Grade: Minimum	**Picloram isooctyl ester** NOEL for systemic effects: 250 mg/kg/day LOEL: 500 mg/kg/day Effects: increased bilirubin (males) and increased BUN (both sexes). Histological changes in the liver were observed at 1000 mg/kg/day (highest dose tested). However, these were attributed to encephalozoon infection. The findings were not confirmed and microscopic examinations were not conducted at the low and mid-dose levels. Therefore, this study was not considered reliable for risk assessment purposes.
870.3700	Developmental study in rats MRID# 41382502 Date: 1/23/90 Core Grade Minimum	**Picloram potassium salt** Maternal NOEL: 174 (150) mg/kg/day Maternal LOEL: 347 (298) mg/kg/day based on excessive salivation. ( ) = acid equivalent

Subchronic, Chronic and Other Toxicity Profile for Picloram		
GDLN	STUDY	RESULTS
		Developmental NOEL: 347 (298) mg/kg/day (HDT)
870.3700	Developmental study in rabbits MRID# 41069501, 00138703 Date: 1/17/84 Core Grade Minimum	**Picloram potassium salt** Maternal NOEL: 40 (34) mg/kg/day Maternal LOEL: 200 (172) mg/kg/day based on reduced maternal weight gain during gestation. ( ) = acid equivalent Developmental NOEL: 400 (340) mg/kg/day (HDT)
870.3700	Developmental study in rats MRID# 41382504 Date: 1/19/90 Core Grade Guideline	**Picloram triisopropanolamine salt** Maternal NOEL: 500 (280) mg/kg/day Maternal LOEL: 1000 (560) mg/kg/day based on excessive salivation, decreased body weight gain and food consumption. ( ) = acid equivalent Developmental NOEL: 1000 (560) mg/kg/day (HDT)
870.3700	Developmental study in rabbits MRID# 42460901 Date: 8/11/92 Core Grade Guideline	**Picloram triisopropanolamine salt** Maternal NOEL: 54 (30) mg/kg/day Maternal LOEL: 180 (101) mg/kg/day based on increased rate of abortions at 1000 (560), increased clinical signs at 538 (301)and above and decreased food consumption & body weight gain at 180 (101) mg/kg/day and above. ( ) = acid equivalent Developmental NOEL: 1000 (560) mg/kg/day (HDT)
870.3700	Developmental study in rats MRID 00030284 Date: 1972 Core Grade Supplementary	**Picloram acid** Maternal NOEL: 500 mg/kg/day Maternal LOEL: 750 mg/kg/day based on hyperactivity and mild diarrhea and deaths. Developmental NOEL: Not attained Developmental LOEL: 500 mg/kg/day (LDT) based on transient delayed ossification of 5th

Subchronic, Chronic and Other Toxicity Profile for Picloram		
GDLN	STUDY	RESULTS
		sternebrae (fetuses but not litters).
870.3700	Developmental Study in rats MRID# 42296901 Date: 11/9/91 Core Grade Guideline	**Picloram isooctyl ester** Maternal NOEL: 100 (68) mg/kg/day Maternal LOEL: 500 (340) mg/kg/day based on decreased body weight gain during early gestation. ( ) = acid equivalent Developmental NOEL: 1000 (680) mg/kg/day (HDT)
870.3700	Developmental Study in rabbits MRID# 42121104 Date: 11/18/91 Core Grade Minimum	**Picloram isooctyl ester** Maternal NOEL: 20 (14) mg/kg/day Maternal LOEL: 100 (68) mg/kg/day based on an increase in incidence of clinical signs (decreased feces at 500 and decreased body weight gain at 100 mg/kg/day and above) ( ) = acid equivalent Developmental NOEL: 500 (340) mg/kg/day (HDT)
870.3800	2-generation reproduction toxicity in rats MRID 42078701 Date: 10/2/91 Core Minimum	**Picloram acid** Systemic NOEL: 200 mg/kg/day Systemic LOEL: 1000 mg/kg/day based on microscopic lesions in male (& some female) kidneys, blood in urine, decreased urine specific gravity, increased absolute & relative kidney weights. Reproductive NOEL: 1000 mg/kg/day (HDT)
870.4100	Chronic feeding study in dogs MRID # 40834301 Date: 1988 Core Grade: Minimum	**Picloram acid** NOEL: 35 mg/kg/day LOEL: 175 mg/kg/day Effects: increased absolute and relative liver weights.
870.4200	Oncogenicity study in	**Picloram acid**

Subchronic, Chronic and Other Toxicity Profile for Picloram		
GDLN	STUDY	RESULTS
	mice MRID # 42619301 Date: 12/24/92 Core Grade: Guideline	NOEL = 500 mg/kg/day LOEL: 1000 mg/kg/day Effects: increased absolute and relative kidney weights in males. There was no evidence of carcinogenicity.
870.4300	Chronic feeding/ carcinogenicity study in rats MRID # 00155940 Date: 1/03/86 Core Grade: Minimum	**Picloram acid** NOEL(systemic): 20 mg/kg/day LOEL (systemic): 60 mg/kg/day based on increased size and altered staining properties of centrilobular hepatocytes and increased absolute and/or relative liver weights in both sexes. Negative for carcinogenicity.
870.4300	Chronic feeding/carcinogencity study in rats MRID # 42619302 Date: 12/22/92 Core Grade: Minimum when taken together with 00155940	**Picloram acid** NOEL (systemic): < 250 mg/kg/day LOEL (systemic): 250 mg/kg/day based on increases in the incidence & severity of glomerulonephritis, blood in the urine, decreased specific gravity of the urine, increased size of hepatocytes that often had altered staining properties, increase in the incidence of unilateral or bilateral renal papillary necrosis & increases in absolute and relative kidney weights. No evidence of increased tumor incidence.
870.5100	Gene mutation assay (Ames assay) MRID 41485902 Date: 1990 Acceptable	**Picloram acid** Picloram acid was evaluated in the Ames test using Salmonella typhimurium. Doses ranged up to 5000 ug/plate, with and without metabolic activation. The test substance did not produce a mutagenic response either in the presence or absence of activation.
870.5100	Gene mutation (Ames test) MRID 41485901 Date: 4/27/90 Acceptable	**Picloram triisopropanolamine salt** Picloram triisopropanolamine salt was evaluated in the Ames test using Salmonella typhimurium. Doses ranged up to 5000 ug/plate, with and without metabolic activation. The test material did not produce a mutagenic response either in the presence or absence of activation.

Subchronic, Chronic and Other Toxicity Profile for Picloram		
GDLN	STUDY	RESULTS
870.5100	Gene Mutation Assay (Ames Test) MRID 42121106 Date: 11/25/91 Acceptable	**Picloram isooctyl ester** Picloram isooctyl ester was evaluated in the Ames test using Salmonella typhimurium. Dosages ranged from 16.7 to 1667 ug/plate in studies with and without S9 activation. The test compound did not induce a mutagenic response in the presence or absence of metabolic activation.
870.5300	Gene mutation assay (mammalian cells) MRID 40072601 Date: 1/1/87 Acceptable	**Picloram acid** Picloram acid was evaluated for gene mutation in mammalian cells (HGPRT/CHO). As evaluated up to toxic levels (750 ug/mL without metabolic activation; 1250 ug/mL with metabolic activation), the compound was found to be negative for inducing forward mutation in Chinese hamster ovary (CHO) cells.
870.5300	Gene mutation assay (mammalian cells) MRID 44164801 Date: 11/12/96 Acceptable	**Picloram acid** CHO/HGPRT+ cells cultured in vitro were exposed to picloram acid (81.8% a.i.) at concentrations of 125 to 1750 µg/mL in the absence of metabolic activation, and from 250 to 4500 µg/mL in the presence of S9 (rat induced S9), and assayed for forward mutation to $HGPRT^-$ in the presence of the selective agent thioguanine which permits mutants to survive but kills normal cells. Ethylmethanesulfonate and 20-methylcholanthrene served as positive controls for the non-activation and activation series, respectively. Picloram did not induce a mutagenic response at doses up to and including those generally associated with severe cytotoxicity, ≥ 1250 µg/mL/-S9; ≥ 3000 µg/mL/+S9 .
870.5300	Gene mutation assay (mammalian cells) MRID 42414001 Date: 6/26/92 Acceptable	**Picloram isooctyl ester** Picloram isooctyl ester was evaluated in two independent Chinese Hamster Ovary Cell HGPRT forward gene mutation assays, one of these with, and the other without, S9 activation. Concentrations of the picloram isooctyl ester

Subchronic, Chronic and Other Toxicity Profile for Picloram		
GDLN	STUDY	RESULTS
		employed in the non-activated trial ranged from 1.25 to 50 ug/mL as conducted in two assays of overlapping dosage range. The second trial, also conducted in two assays of overlapping dose and including S9 activation, utilized dosages ranging from 2.50 to 200 ug/mL. Concentrations ≥ 40 ug/mL in the non-activated trial and ≥ 125 ug/mL in the activated trial were severely cytotoxic. There was no evidence of a mutagenic response at any dosage level in either the S9 activated trial(s)/or the non-activated trial(s).
870.5375	Structural Chromosomal Aberration Assay In vitro MRID 42368701 Date: 5/13/92 Acceptable	**Picloram isooctyl ester** Picloram isooctyl ester was evaluated in two independent rat lymphocyte cytogenetic assays with and without S9 activation. Concentrations ranging from 2.67 to 800 ug/mL +/-S9 were assayed in Trial 1; severe cytotoxicity was observed at levels ≥ 80 ug/mL +/-S9. In Trial 2, no cytotoxicity was seen in cells exposed to 8.04 or 17.4 ug/mL +/-S9 and harvested at 24 hours. However, reductions in the mitotic index (MI) were observed in cells harvested 24 or 48 hours post-exposure to 26.8 ug/mL +/-S9. Although a number of minor deficiencies rendered the purported negative results of this study inadequate in initial review, subsequent re-evaluation with additional information and data supplied by the performing laboratory were adequate to upgrade this assay to fully acceptable in demonstrating no potential for inducing chromosomal aberrations.
870.5385	Cytogenetics in vivo MRID 00098322 Date: 12/29/76 Acceptable	**Picloram acid** Picloram acid was evaluated for cytogenetic effects on bone marrow cells of rats via intragastric administration at dosage levels of 0 (vehicle), 20, 200 or 2000 mg/kg. The test material did not produce cytogenetic effects in the study.
870.5395	Cytogenetics assay in	**Picloram triisopropanolamine salt**

Subchronic, Chronic and Other Toxicity Profile for Picloram		
GDLN	STUDY	RESULTS
	vivo MRID 41539701 Date: 5/23/90 Acceptable	Picloram triisopropanolamine salt was evaluated by oral administration to mice in the mouse bone marrow micronucleus test, at dosage levels of 0, 300, 1000 and 3000 mg/kg. The test agent was determined to be non-clastogenic in mice, as determined by lack of mutagenic effect at doses up to lethality (3000 mg/kg).
870.5395	Micronucleus Test in mice MRID 42171602 Date: 12/05/91 Acceptable	**Picloram isooctyl ester** Picloram isooctyl ester was evaluated in the mouse micronucleus assay at single oral gavage doses of 0 (2 control groups), 500, 1667 and 5000 mg/kg (limit dose) using 24, 48 and 72 hour sacrifice times. The material was found not to be clastogenic. No lethality was reported and there was no evidence of target tissue cytotoxicity. The picloram compound was tested at a sufficiently high level and found not to be clastogenic.
870.5550	Other genotoxic effects (UDS DNA synthesis) MRID # 41549701 Date: 6/21/90 Acceptable	**Picloram acid** Picloram acid was evaluated for genotoxic potential as administered to primary rat hepatocyte cultures at concentrations of 0 (vehicle), 10, 33.3, 100, 333.3 or 1000 ug/mL. The test material was negative for unscheduled DNA synthesis (UDS, a measure of DNA damage/repair) treated up to cytotoxic levels of (1000 ug/ml).
870.5550	Other genotoxic effects (UDS DNA synthesis) MRID 41539702 Date: 6/1/90 Acceptable	**Picloram triisopropanolamine salt** Picloram triisopropanolamine was evaluated for genotoxic (DNA damage/repair) potential when administered to primary rat hepatocyte cultures at concentrations up to 1500 ug/mL. The test material was negative for inducing unscheduled DNA synthesis (UDS) at doses up to toxic levels (1500 ug/mL).
870.7485	Metabolism MRID 41209602 Date: 8/1/89	**Picloram acid** The absorption, distribution, metabolism and excretion of picloram acid was evaluated in

Subchronic, Chronic and Other Toxicity Profile for Picloram		
GDLN	STUDY	RESULTS
	Acceptable in conjunction with MRID 00098321	female rats administered a single i.v. or oral gavage dose of 10 mg/kg, an oral gavage dose of 1000 mg/kg ^{14}C-picloram, or 1 mg/kg/day unlabeled picloram by gavage for 14 days followed by a single oral gavage dose of 10 mg/kg ^{14}C-picloram on day 15. The study demonstrates that ^{14}C-picloram is rapidly absorbed, distributed and excreted following oral and i.v. administration.
870.7485	Metabolism MRID 00098321 Date: 2/4/80 Acceptable in conjunction with MRID 41209602	**Picloram acid** Fischer 344 rats were administered 14 & 160 mg/kg i.v. (9.6 & 1634 mg/kg oral). With the 14 mg/kg i.v. dose plasma, the clearance was 34.3 mL/kg/min actively secreted. 98.4% excreted unchanged in 72 hours. 85% excreted in urine in 48 hours. I.V. and oral levels of 9.6 and 1634 mg/kg showed excretion of 84.4% in the urine and 0.04 to 6.48% in tissue.
870.7485	Metabolism MRID 42171603 Date: 12/23/91 Acceptable	**Picloram acid** The absorption, metabolism and excretion of picloram isooctyl ester (also referred to as picloram ethylhexyl ester) was studied in male F344 rats following single oral (gavage) dosing with 15 mg/kg of ^{14}C-picloram isooctyl ester. The ester was absorbed and excreted rapidly. By 48 hours post-exposure, mean recovery of radioactivity was 96.4%. The urine was the major elimination route (68 % of administered dose). The feces and expired $^{14}CO_2$ represented 16.35% and 10.16%, respectively, of the administered dose. Elimination of picloram ethylhexyl ester was rapid, as indicated by 67% recovery at 24 hours post-dosing. The major metabolite was 2-ethyl-1, 6-hexanoic acid. This study supports that picloram ethylhexyl ester is hydrolyzed rapidly to picloram (free acid) and 2-ethyl hexanol, and that picloram ethylhexyl ester does not influence the excretion of picloram in the rat.

Subchronic, Chronic and Other Toxicity Profile for Picloram		
GDLN	STUDY	RESULTS
870.7485	Metabolism MRID 42343101 Date: 5/26/92 Acceptable	**Picloram acid** The absorption, metabolism and excretion of picloram triisopropanolamine salt was studied in male F344 rats following administration of single oral doses (gavage) of 9.5 mg/kg of C^{14}-triisopropanolamine and 9.8 mg/kg of picloram. This level of dosing delivered 20-30 μCi per animal in the forms of ^{14}C-triisopropanolamine. The ^{14}C-triisopropanolamine was absorbed readily, with peak plasma radioactivity being observed at 0.25 hours post-dosing. The administered dose of radioactivity as recovered primarily in urine, feces, expired carbon dioxide, tissue/carcass and final cage rinse was 94%. Unchanged triisopropanolamine accounted for 80% of the total radioactivity excreted in the urine. No other metabolites were identified in the 0-6 hour pooled urine sample. The data suggest that the conversion of picloram triisopropanolamine salt to picloram was not affected by the presence of triisopropanolamine.

Attachment 5: Active and Conditional Registrations

Picloram – PC Code 005101							
Registration #	**Name**	**Status**	**Restricted Use Product**	**Company #**	**Company Name**	**Percent Active Ingredient**	**Active Ingredient**
228-586	TROPPER EXTRA SELECTIVE HERBICIDE	Conditionally Registered (19-Nov-2008)	Y	228	NUFARM AMERICAS, INC.	10.2	Picloram
62719-653	Grazon HL	Registered (07-Mar-2013)	Y	62719	DOW AGROSCIENCES LLC	14.44	Picloram
62719-655	GF-2766	Registered (05-Mar-2013)	Y	62719	DOW AGROSCIENCES LLC	14.44	Picloram
83558-15	TECHNICAL PICLORAM	Registered (23-Feb-2009)	N	83558	CELSIUS PROPERTY B.V., AMSTERDAM (NL)	95.1	Picloram

Picloram, triisopropanolamine salt – PC Code 005102							
Registration #	**Name**	**Status**	**Restricted Use Product**	**Company #**	**Company Name**	**Percent Active Ingredient**	**Active Ingredient**
228-530	MANPOWER HERBICIDE	Conditionally Registered (17-Aug-2007)	Y	228	NUFARM AMERICAS, INC.	10.2	Picloram, triisopropanolamine salt
228-599	TROOPER PRO HERBICIDE	Registered (01-Apr-2009)	Y	228	NUFARM AMERICAS, INC.	19.42	Picloram, triisopropanolamine salt
42750-80	PICLORAM + 2,4-D RANGELAND	Conditionally Registered (01-Jun-2005)	Y	42750	ALBAUGH INC	10.2	Picloram, triisopropanolamine salt
42750-82	PICLORAM + 2,4-D IVM	Conditionally Registered (01-Jun-2005)	Y	42750	ALBAUGH INC	10.2	Picloram, triisopropanolamine salt
42750-83	PICLORAM + 2,4-D RTU	Conditionally Registered (01-Jun-2005)	N	42750	ALBAUGH INC	5.4	Picloram, triisopropanolamine salt
42750-107	PD 2	Conditionally Registered (16-Dec-2005)	Y	42750	ALBAUGH INC	10.2	Picloram, triisopropanolamine salt
48273-15	TORAM 101	Conditionally Registered (05-Aug-	Y	48273	MARMAN USA INC	10.2	Picloram, triisopropanolamine salt

Picloram, triisopropanolamine salt – PC Code 005102							
Registration #	**Name**	**Status**	**Restricted Use Product**	**Company #**	**Company Name**	**Percent Active Ingredient**	**Active Ingredient**
		1996)					
53883-255	PICLORAM 10.2 HERBICIDE	Conditionally Registered (12-Feb-2009)	Y	53883	CONTROL SOLUTIONS, INC.	10.2	Picloram, triisopropanolamine salt
62719-5	TORDON 101 MIXTURE	Registered (04-Dec-1989)	Y	62719	DOW AGROSCIENCES LLC	10.2	Picloram, triisopropanolamine salt
62719-31	TORDON 101R	Conditionally Reregistered (11-May-1998)	N	62719	DOW AGROSCIENCES LLC	5.4	Picloram, triisopropanolamine salt
62719-182	GRAZON P+D	Conditionally Registered (21-Nov-1990)	Y	62719	DOW AGROSCIENCES LLC	10.2	Picloram, triisopropanolamine salt
62719-480	SURMOUNT	Registered (09-Jun-2004)	Y	62719	DOW AGROSCIENCES LLC	13.24	Picloram, triisopropanolamine salt
62719-571	GRAZON PD2	Conditionally Registered (20-Apr-2007)	Y	62719	DOW AGROSCIENCES LLC	9.13	Picloram, triisopropanolamine salt
81927-15	ALLIGARE	Conditionally	N	81927	ALLIGARE, LLC	5.4	Picloram,

Picloram, triisopropanolamine salt – PC Code 005102							
Registration #	**Name**	**Status**	**Restricted Use Product**	**Company #**	**Company Name**	**Percent Active Ingredient**	**Active Ingredient**
	PICLORAM + D RTU	Registered (24-Aug-2007)					triisopropanolamine salt
81927-16	ALLIGARE PICLORAM+D	Conditionally Registered (31-Aug-2007)	Y	81927	ALLIGARE, LLC	10.2	Picloram, triisopropanolamine salt

PC code 005104 – picloram-potassium							
Registration #	**Name**	**Status**	**Restricted Use Product**	**Company #**	**Company Name**	**Percent Active Ingredient**	**Active Ingredient**
228-535	TROOPER 22K HERBICIDE	Registered (06-Dec-2007)	Y	228	NUFARM AMERICAS, INC.	24.4	Picloram-potassium
42750-79	PICLORAM K-SALT RANGELAND	Conditionally Registered (23-Jun-2005)	Y	42750	ALBAUGH INC	24.4	Picloram-potassium
42750-81	PICLORAM K-SALT IVM	Conditionally Registered (23-Jun-2005)	Y	42750	ALBAUGH INC	24.4	Picloram-potassium
62719-6	TORDON 22K SPECIALTY HERBICIDE	Reregistered (10-Mar-1998)	Y	62719	DOW AGROSCIENCES LLC	24.4	Picloram-potassium
62719-17	TORDON K	Reregistered (10-Mar-1998)	Y	62719	DOW AGROSCIENCES LLC	24.4	Picloram-potassium
62719-30	TORDON K SALT LIQUOR	Registered (04-Dec-1989)	N	62719	DOW AGROSCIENCES LLC	34.7	Picloram-potassium
62719-181	GRAZON PC	Reregistered (21-Dec-1998)	Y	62719	DOW AGROSCIENCES LLC	24.4	Picloram-potassium
62719-528	GF-1249	Conditionally Registered (15-Nov-2005)	Y	62719	DOW AGROSCIENCES LLC	4.07	Picloram-potassium

PC code 005104 – picloram-potassium							
Registration #	**Name**	**Status**	**Restricted Use Product**	**Company #**	**Company Name**	**Percent Active Ingredient**	**Active Ingredient**
62719-528	GF-1249	Conditionally Registered (15-Nov-2005)	Y	62719	DOW AGROSCIENCES LLC	22.2	Triclopyr, triethylamine salt
81927-17	ALLIGARE PICLORAM K	Registered (23-Aug-2007)	Y	81927	ALLIGARE, LLC	24.4	Picloram-potassium
81927-18	ALLIGARE PICLORAM 22K	Registered (23-Aug-2007)	Y	81927	ALLIGARE, LLC	24.4	Picloram-potassium